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MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/760,819	STANLEY, CHRISTOPHER J.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2005* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-26 and 28-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-26 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2001 (original)* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/313,385* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE and the amendment filed on March 30, 2005 have been entered. The claims pending in this application are claims 1, 3-26, and 28-34. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on March 30, 2005.

Claim Objections

2. Claim 3 is objected to because of the following informalities: "the carrier" in line 7 of the claim should be "said non-nucleotide carrier macromolecule".

3. Claim 5 is objected to because of the following informalities: "said carrier molecule" should be "said carrier macromolecule".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 5, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed composition/or methods are not described in the instant disclosure, claims 5, 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Independent claim 18 requires that a first nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons hybridizes a second nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons. Although the specification describes that a nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (e.g., see page 3, second paragraph), the specification fails to define or provide any disclosure to support that a first nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons hybridizes a second nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons as recited in claim 18. Furthermore, the specification does not provide a carrier macromolecule has a peak molecular weight of 4,000,000 Dalton as recited in claim 5 although the specification

provides different ranges for molecular weight of a carrier macromolecule (see pages 3, 9, and 10).

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Landegren *et al.*, (US Patent NO. 4,988,617, published on January 29, 1991).

Landegren *et al.*, teach method of detecting a nucleotide change in nucleic acids.

Regarding claim 1, Landegren *et al.*, teach a method comprising: (a) annealing a labeled oligonucleotide target probe of predetermined sequence to a first sequence of a test substance so

that said target nucleotide position is aligned with a nucleotide in an end region of the target probe; (b) annealing a labeled adjacent oligonucleotide probe of predetermined sequence to a second sequence of said test substance contiguous to said first test substance sequence, so that the end region of said target probe is directly adjacent to said adjacent probe; (c) contacting said annealed target and adjacent probes with a linking agent such as a ligase under conditions such that the directly adjacent ends of said probes would link to form a linked probe product unless there is nucleotide base pair mismatch between the target probe and test substance at the target nucleotide position; (d) separating said test substance from said annealed probes, and (e) detecting whether or not linking occurs as an indication of nucleotide base pair matching or mismatching at said target nucleotide position (see Figure 1 and column 3, lines 1-20) wherein these labels on oligonucleotide target and adjacent probes are fluorescent tags such as fluorescein coupling to a 5' aminothymidine in the probe (see column 8, lines 43-62), Landegren *et al.*, disclose providing a primer (ie., the oligonucleotide target probe) covalently bound to a non-nucleotide carrier macromolecule (ie., fluorescein), hybridizing the bound primer to said template (ie., the first sequence of a test substance); and extending said primer to form an extended primer (ie., the linked probe product) as recited in the claim. Since fluorescein has OH-group and is water soluble (see attachment for fluorescein) and the specification does not define "macromolecule" and it is known that OH- group is a nucleophilic functional group, Landegren *et al.*, disclose said carrier macromolecule (ie., fluorescein) is water soluble at a temperature in the range of 0-60°C wherein said carrier macromolecule is a synthetic polymer having nucleophilic functional groups as recited in the claim.

Therefore, Landegren *et al.*, teach all limitations recited in claim 1.

8. Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Bronstein (US Patent No. 5,220,005, published on June 15, 1993).

Regarding claim 18, Bronstein teaches to hybridize a DNA probe labeled with alkaline phosphatase with nucleic acids immobilized on a nitrocellulose membrane and detect the hybridization (see column 13, lines 44-61). Since alkaline phosphatase is directly and covalently attached to the DNA probe and it is known that alkaline phosphatase has a molecular weight in excess of 80,000 Daltons, the DNA probe taught by Bronstein is a first nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (ie., alkaline phosphatase) as recited in the claim. Since it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a formula of ($C_6H_{12}O_6$) with a molecular weight of 180.2 Daltons (see an attachment for cellulose in previous office action mailed on January 7, 2004), a nucleic acid that is complementary with the DNA probe and is immobilized on a nitrocellulose membrane is a second nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (3,000 ×180.2=540,600 Daltons) as recited in the claim. Since Bronstein teaches to hybridize a DNA probe labeled with alkaline phosphatase with nucleic acids immobilized on a nitrocellulose membrane and detect the hybridization (see column 13, lines 44-61), Bronstein discloses contacting said first and second nucleic acids under hybridization conditions and detecting hybridization between said first and second nucleic acids as recited in the claim.

Therefore, Bronstein teaches all limitations recited in claim 18.

Response to Arguments

In page 9, third paragraph bridging to page 10, first paragraph of applicant's remarks, applicant argues that "[B]ronstein Does Not Anticipate Claim 18 Because Bronstein Does Not Disclose a First Nucleic Acid Bound to a Non-Nucleotide Carrier Macromolecule And a Second Nucleic Acid Bound to a Non-Nucleotide Carrier Macromolecule".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. Since alkaline phosphatase is directly and covalently attached to the DNA probe and it is known that alkaline phosphatase has a molecular weight in excess of 80,000 Daltons, the DNA probe taught by Bronstein is a first nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (ie., alkaline phosphatase). Since it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a formula of ($C_6H_{12}O_6$) with a molecular weight of 180.2 Daltons (see an attachment for cellulose in previous office action mailed on January 7, 2004), a nucleic acid taught by Bronstein that is complementary with the DNA probe and is immobilized on a nitrocellulose membrane is a second nucleic acid bound to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (3,000 ×180.2=540,600 Daltons).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 3, 4, 7-9, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.,* (US Patent No. 5,4870,723, filed on August 23, 1993) in view of Gold *et al.,* (US Patent NO. 6,011,020, filed on May 4, 1995).

Regarding claim 3, Walker *et al.,* teach polymerase extension of a labeled primer specifically hybridized to a target or control sequence wherein the label is alkaline phosphatase (see column 9, first and second paragraphs), Walker *et al.,* disclose providing a primer bound to a non-nucleotide carrier macromolecule (ie., alkaline phosphatase), hybridizing the bound primer to said template (ie., the target or control sequence); and extending said primer to form an extended primer (ie., the extension product of the labeled primer) which replicates from said template wherein the carrier is a polypeptide (ie., alkaline phosphatase) as recited in the claim.

Walker *et al.,* teach that said primer is extended by a polymerase wherein said polymerase incorporates nucleotides into said primer wherein said primer is extended in a strand displacement amplification and said template is a double stranded template and is denatured to a single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of one of the template strands and a second primer is provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand as recited in claims 8, 9, and 11 (see Figure 1 and columns 10-12 of Example 1). Since the specification does not define "carrier macromolecule" and Walker teaches to use one or more detectable markers including enzymes and avidin (column 9, first paragraph), it is obvious to one having ordinary skill in the art at the time the invention was made to label a second primer with a carrier macromolecule as recited in claims 13.

Walker *et al.,* do not disclose a primer covalently bound to a carrier macromolecule via one or more moieties derived from divinyl sulfone as recited in claims 3 and 7.

Gold *et al.,* teach a nucleic acid covalently bound to a carrier macromolecule (ie., Dextran) via one or more moieties derived from divinyl sulfone (see column 8, fourth paragraph and column 18, second paragraph).

Regarding claim 4, since it is known that dextran is a linear polysaccharide made of many glucose molecules joined into a long chain and dextran/salt solutions are sometimes used to replace lost blood in emergency situation (see attachment for dextran), dextran must be water soluble with pH of 4-10. Thus Gold *et al.,* disclose that the carrier macromolecule (ie., dextran) in its free state is substantially linear and substantially charged at a pH in the range of 4 to 10 as recited in claim 4.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 using a primer covalently bound to a carrier macromolecule (ie., dextran) via one or more moieties derived from divinyl sulfone in view of the patents of Walker *et al.,* and Gold *et al.*. One having ordinary skill in the art would have been motivated to do so because Gold *et al.,* have successfully made a nucleic acid covalently bound to a carrier macromolecule (ie., dextran) via one or more moieties derived from divinyl sulfone and the simple replacement of one well known label (ie., alkaline phosphatase) from another well known label (i.e., dextran) during the process for making a primer recited in claim 3 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time

the invention was made because both alkaline phosphatase and dextran are used as oligonucleotide labels.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claims 10, 12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.,* (1993) in view of Gold *et al.,* (1995) as applied to claim 1, 3, 4, 7-9, 11, and 13, and above, and further in view of Landegren *et al.,* (US Patent No. 4,988,617, published on January 29, 1991).

The teachings of Walker *et al.,* and Gold *et al.,* have been summarized previously, *supra*.

Walker *et al.,* and Gold *et al.,* do not disclose that said primer is extended by the action of a ligase ligating said primer to at least one another primer hybridized to said template as recited in claim 10, said carrier macromolecule is bound to a solid support as recited in claim 12, said another primer which is ligated by said ligase is also bound to a carrier macromolecule wherein during the extension, a detectable marker is incorporated into one of the extended primers as recited in claims 14 and 15, said extension of one of the primers is conducted *in situ* in a

biological sample wherein said biological sample is a plant or animal tissue sample, microorganism culture, or microorganism culture medium as recited in claims 16 and 17.

Landegren *et al.*, teach a ligase chain reaction using two primers with different labels (see Figure 1, column 4, lines 12-50 , column 8, lines 43-46, and column 10, last paragraph). Since the specification does not define "carrier macromolecule" and biotin on one of the primers taught by Landegren *et al.*, is a carrier molecule and a detectable marker as recited in claims 14 and 15. Therefore, Landegren *et al.*, teach that said primer is extended by the action of a ligase ligating said primer to at least one another primer hybridized to said template as recited in claim 10, said another primer which is ligated by said ligase is also bound to a carrier macromolecule wherein during the extension, a detectable marker is incorporated into one of the extended primers as recited in claims 14 and 15. Since Landegren *et al.*, teach that, after ligation, the ligation product labeled with biotin is purified by streptavidin immobilized to a solid support (see columns 10 and 11), in view of teachings of Landegren *et al.*, Walker and Gold *et al.*, said carrier macromolecule (ie., dextran) taught by Gold *et al.*, is bound to a solid support as recited in claim 12. Since Landegren *et al.*, teach to use DNA from sickle cell patient for in situ analysis, Landegren *et al.*, disclose that said extension of one of the primers is conducted *in situ* in a biological sample wherein said biological sample is an animal tissue sample as recited in claims 16 and 17.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 10, 14, and 15 in view of the patents of Walker *et al.*, Gold *et al.*, and Landegren *et al.*, One having ordinary skill in the art would have been motivated to do so because Landegren *et al.*, have successfully

extended a primer by ligase chain reaction using two primers with different labels and the simple replacement of one well known replication method (i.e., the method taught by Walker *et al.*,) from another well known replication method (i.e., the method taught by Landegren *et al.*,) during the process of performing the methods recited in claims 10, 12, and 14-17 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Walker and the method taught by Landegren *et al.*, are functional equivalent methods which are used for the same purpose (ie., extending a primer).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

12. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.*, (1993) in view of Gold *et al.*, (1995) as applied to claim 1, 3, 4, 7-9, 11, and 13 above, and further in view of in view of Yamane *et al.*, (US Patent No. 4,876,335, published on October 24, 1989).

The teachings of Walker *et al.*, and Gold *et al.*, have been summarized previously, *supra*.

Walker *et al.*, and Gold *et al.*, do not disclose that said carrier macromolecule is a homopolyamino acid.

Yamane *et al.,* teach to use a polylysine-labeled oligonucleotide for hybridization (see abstract). Lysine residues on the polylysine can be any desired numbers wherein the polylysine is covalently connected to the oligonucleotide (see column 2).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 34 wherein the said carrier macromolecule is a homopolyamino acid (ie., polylysine) in view of the patents of Walker *et al.,* Gold *et al.,* and Yamane *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of label (ie., polypeptide taught by Gold *et al.,*) from another kind of label (i.e., polylysine taught by Yamane *et al.,*) during the process for making a primer recited in claim 34 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made used as because the replacement would enhance the hybridization between the nucleic acid template and the primer since polylysine-labeled oligonucleotide taught by Yamane *et al.,* carries positive charges.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

13. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.*, (1993) in view of Gold *et al.*, (1995) and Landegren *et al.*, (1991) as applied to claim 1, 3, 4, and 7-17 above, and further in view of Barany *et al.*, (US Patent NO. 6,027,889, priority date: May 28, 1996).

The teachings of Walker *et al.*, Gold *et al.*, and Landegren *et al.*, have been summarized previously, *supra*.

Walker *et al.*, Gold *et al.*, and Landegren *et al.*, do not disclose using the probe to detect the nucleic acid sequence in a sample by hybridization thereto as recited in claim 20 However, as shown above, Walker *et al.*, in view of Gold *et al.*, and Landegren *et al.*, teach making a probe for detecting said sequence by using said sequence as a template sequence in the method as claimed in claim 17 such that a probe comprises said extended primer that has a sequence complementary to said sequence to be detected is bound to said carrier macromolecule, removing any free nucleic acid not bound to said carrier macromolecule thereof as recited in claim 20.

Barany *et al.*, teach using the ligated probe to detect the nucleic acid sequence in a sample by hybridization (see Figure 1).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method in view of the patents of Walker *et al.*, Gold *et al.*, Landegren *et al.*, and Barany *et al.*. One having ordinary skill in the art would have been motivated to do so because Barany *et al.*, have successfully used a ligated product as a probe for a hybridization assay (see Figure 1). One having ordinary skill in the art

at the time the invention was made would have been a reasonable expectation of success to use a ligated product recited in claim 17 as a probe for a hybridization assay.

14. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gold *et al.,* (US Patent NO. 6,011,020, filed on May 4, 1995).

Regarding claim 21, since Gold *et al.,* teach to bind a complex formed by a nucleic acid and a PEG molecule to an ion exchange chromatography wherein the nucleic acid binds a PEG molecule by vinyl sulfone (see column 18, second paragraph and column 31, second paragraph) and PEG is synthethic polymer having nucleophilic functional groups (see the specification, page 8), Gold *et al.,* disclose an immobilized nucleic acid comprising a nucleic acid linked via one or more moieties derived from vinyl sulfone to a non-nucleotide carrier macromolecule (ie.,PEG), which the non-nucleotide carrier macromolecule is directly bound to a solid support (ie., the desalting chromatography taught by Gold *et al.,*) as recited in claim 21.

Gold *et al.,* do not disclose that a non-nucleotide carrier macromolecule is dextran. However, Gold *et al.,* teach that different non-immunogenic, high molecular weight compounds such as PEG and dextran are used to modify a nucleic acid ligand (see column 8, lines 45-53 and column 18, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made an immobilized nucleic acid comprising a nucleic acid linked via one or more moieties derived from vinyl sulfone to a non-nucleotide carrier macromolecule such as dextran which the non-nucleotide carrier macromolecule is directly bound to a solid support recited in claim 3 in view of the patent of Gold *et al.*. One

having ordinary skill in the art would have been motivated to do so because Gold *et al.,* have successfully made a nucleic acid covalently bound to a carrier macromolecule (ie., dextran) via one or more moieties derived from divinyl sulfone and the simple replacement of one kind of non-immunogenic, high molecular weight compound (ie., PEG) from another kind of non-immunogenic, high molecular weight compound (ie., dextran) during the process for making an immobilized nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because both PEG and dextran are non-immunogenic, high molecular weight compounds and are used to modify a nucleic acid and they are exchangeable (see column 8, lines 45-53).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

15. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gold *et al.,* (1995) as applied to claim 21 above, and further in view of Urdea (US Patent No. 4,775,619, published on October 4, 1988).

The teachings of Gold *et al.,* have been summarized previously, *supra*.

Gold *et al.,* do not disclose formulating the immobilized nucleic acid recited in claim 21

as a hybridization probe and introducing the immobilized nucleic acid into a hybridization utilizing the hybridization probe as recited in claim 22.

Urdea teaches to perform a hybridization of a nucleic acid immobilized on a column to a sample containing a DNA fragment (see column 10, lines 40-58).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have formulated the immobilized nucleic acid recited in claim 21 as a hybridization probe and introduced the immobilized nucleic acid into a hybridization utilizing the hybridization probe in view of the patents of Gold *et al.*, and Urdea. One having ordinary skill in the art would have been motivated to do so because Urdea indicates that a nucleic acid immobilized on a column is used for hybridization with a sample containing a DNA fragment (see column 10, lines 40-58). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to formulate the immobilized nucleic acid recited in claim 21 as a hybridization probe and introduce the immobilized nucleic acid into a hybridization utilizing the hybridization probe.

16. Claims 3-6, 8, 9, 11, 13, and 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.*, (1993) in view of Westling *et al.*, (US Patent No. 5,700,921, filed on November 27, 1995).

The teachings of Walker *et al.*, have been summarized previously, *supra*.

Regarding claim 4-6, since Walker teaches adding a mixture comprising a nucleic acid polymerase, dNTPs and at least one primer which is complementary to a region at the 3' end of a target fragment, and allowing the mixture to react for a time sufficient to generate reaction

products (see Figure 1 and Example 1 in columns 10-12) wherein the at least primer is labeled with alkaline phosphatase (see column 9, first paragraph), and it is known that alkaline phosphatase has a molecular weight in excess of 80,000 Daltons, and is water soluble with a pH of 7.6 (see attachment for alkaline phosphatase in the office action mailed on July 1, 2004), Walker *et al.,* disclose that the carrier macromolecule (ie., alkaline phosphatase) in its free state is substantially linear and substantially uncharged at a pH in the range of 4 to 10 wherein said carrier molecule has a peak molecular weight in the range of in excess of 80,000 to 4,000,000 Daltons and said carrier macromolecule has a molecular weight in excess of 80,000 Daltons as recited in claims 4-6 wherein alkaline phosphatase is a polypeptide as recited in claim 34.

Regarding claims 8, 9, 11, and 13, Walker *et al.,* teach that said primer is extended by a polymerase wherein said polymerase incorporates nucleotides into said primer wherein said primer is extended in a strand displacement amplification and said template is a double stranded template and is denatured to a single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of one of the template strands and a second primer is provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand as recited in claims 8, 9, and 11 (see Figure 1 and Example 1 in columns 10-12). Since the specification does not define "carrier macromolecule" and Walker teaches to use one or more detectable markers including enzymes and avidin (see column 9, first paragraph), it is obvious to one having ordinary skill in the art at the time the invention was made to label a second primer with a carrier macromolecule as recited in claims 13.

Walker *et al.,* do not disclose a primer bound to a carrier macromolecule via one or more moieties derived from divinyl sulfone wherein alkaline phosphatase is a polypeptide as recited in claims 3 and 23.

Westling *et al.,* teach that an oligonculeotide is bound to said carrier macromolecule(ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone (see columns 10 and 11).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 3 and 23 wherein said primer is bound to said carrier macromolecule (ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone in view of the patents of Walker *et al.,* and Westling *et al.*. One having ordinary skill in the art would have been motivated to do so because Westling *et al.,* have successfully bound an oligonculeotide to a carrier macromolecule (ie., alkaline phosphatase) via one or more moieties derived from divinyl sulphone, and the simple replacement of one well known method (i.e., the method taught by Walker *et al.,*) from another well known method (i.e., the method taught by Westling *et al.,*) during the process of bonding a primer to a carrier macromolecule(ie., alkaline phosphatase) would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because bonding a primer to a carrier macromolecule taught by Walker *et al.,* and bonding a primer to a carrier macromolecule taught by Westling *et al.*, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their

expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

17. Claims 24-26, 28, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.*, (1993) and Westling *et al.*, (1995) as applied to claims 1, 3-6, 8, 9, 11, 13, and 23 above, and further in view of Lihme *et al.*, (WO 93/01498, published on January 21, 1993).

The teachings of Walker *et al.*, and Westling *et al.*, have been summarized previously, *supra*.

Regarding claims 28 and 30, Walker *et al.*, teach that said primer is extended in a strand displacement amplification and said template is a double stranded template and is denatured to a single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of one of the template strands and a second primer is provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand as recited in claims 28 and 30 (see Figure 1 and Example 1 in columns 10-12).

Walker *et al.*, and Westling *et al.*, do not disclose a primer bound to dextran as recited in claim 24.

Regarding claim 24-26, Lihme *et al.*, teach that a water-soluble polymeric carriers such as dextran having covalently attached one or more moieties derived from divinyl sulfone is capable of reaction with an oligonucleotide having a functional group which is reactive towards said free vinyl group wherein said dextran in its free state is substantially linear and substantially unchanged at a pH in the range of 4 to 10 wherein said dextran has a peak molecular weight in

the range of 1,000 to 40,000,000 (see claim 1 in page 114 and claim 18 in page 116 and page 20).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 24-26, 28, and 30 in view of the references of Walker *et al.*, Westling *et al.,* and Lihme *et al.*. One having ordinary skill in the art would have been motivated to do so because Lihme *et al.,* suggest to incorporate a water-soluble polymeric carriers having covalently attached one or more moieties derived from divinyl sulfone (ie., dextran) to an oligonucleotide having a functional group which is reactive towards said free vinyl group (see claim 1 in page 114 and claim 18 in page 116) and the simple replacement of one kind of water-soluble polymeric carriers (i.e., alkaline phosphatase taught by Westling *et al.,*) from another kind of water-soluble polymeric carriers (i.e., dextran taught by Lihme *et al.,*) during the process of bonding a primer to a carrier macromolecule would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because both alkaline phosphatase and sugar (i.e., dextran) covalently link to a nucleic acid by derivation of divinyl sulfone and are exchangeable (see Lihme *et al.,* column 11).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

18. Claims 29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker *et al.,* in view of Westling *et al.,* and Lihme *et al.,* as applied to claims 3-6, 8, 9, 11, 13, 23, 24-26, 28, and 30 above, and further in view of Landegren *et al.,* (US Patent No. 4,988,617, published on January 29, 1991).

The teachings of Walker *et al.*, Westling *et al.,* and Lihme *et al.,* have been summarized previously, *supra*.

Walker *et al.,* and Gold *et al.,* do not disclose that said primer is extended by the action of a ligase ligating said primer to at least one further primer hybridized to said template as recited in claim 29, said carrier macromolecule is bound to a solid support as recited in claim 31, and said extension of one of the primers is conducted *in situ* in a biological sample wherein said biological sample is a plant or animal tissue sample, microorganism culture, or microorganism culture medium as recited in claims 32 and 33.

Landegren *et al.,* teach a ligase chain reaction using two primers with different labels (see Figure 1, column 4, lines 12-50, column 8, lines 43-46, and column 10, last paragraph). Therefore, Landegren *et al.,* teach that said primer is extended by the action of a ligase ligating said primer to at least one another primer hybridized to said template as recited in claim 29. Since Landegren *et al.,* teach that, after ligation, the ligation product labeled with biotin is purified by streptavidin immobilized to a solid support (see columns 10 and 11), in view of

teachings of Landegren *et al.,* Walker *et al.*, Westling *et al.,* and Lihme *et al.,* said carrier macromolecule (ie., dextran) taught by Lihme *et al.,* is bound to a solid support as recited in claim 31. Since Landegren *et al.,* teach to use DNA from sickle cell patient for in situ analysis, Landegren *et al.,* disclose that said extension of one of the primers is conducted in situ in a biological sample wherein said biological sample is an animal tissue sample as recited in claims 32 and 33.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 29 and 31-33 in view of the patents of Walker *et al.,*, Westling *et al.,* Lihme *et al.,* and Landegren *et al.,* One having ordinary skill in the art would have been motivated to do so because Landegren *et al.,* have successfully extended a primer by ligase chain reaction using two primers with different labels and the simple replacement of one well known replication method (i.e., the method taught by Walker) from another well known replication method (i.e., the method taught by Landegren *et al.,*) during the process of performing the methods recited in claims 29 and 31-33 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Walker and the method taught by Landegren *et al.,* are functional equivalent methods which are used for the same purpose (ie., extending a primer).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

19. Applicant's arguments with respect to claims 1, 3-17, 19-26, and 28-34 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

20. No claim is allowed.

21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
May 17, 2005

FRANK LU
PATENT EXAMINER